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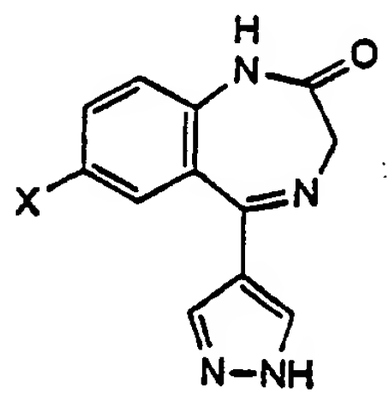
(54) Title: BENZODIAZEPINONES AND MEDICINES CONTAINING THEM



(I)

(57) Abstract

Novel benzodiazepinones of formula (I) wherein X is Cl or CH_3, and compositions containing same for alleviation of viral infections, including HIV infections.

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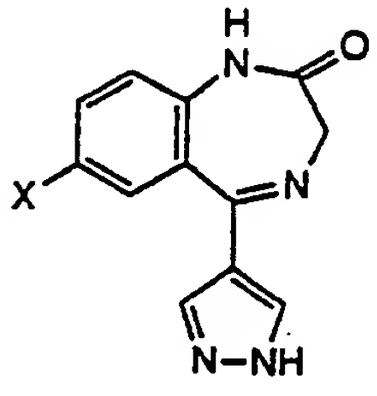
Benzodiazepinones and medicines containing them

The present invention relates to benzodiazepinones of formula



I

wherein X is Cl or CH_3,

and pharmaceutically acceptable salts.

Objects of the present invention are the above compounds per se and for use as a therapeutically active agent, especially for the treatment or prophylaxis of viral infections, particularly of retroviral infections, such as HIV 1 and/or HIV 2 infections, or for protecting cells against such infections;

further a process for the manufacture of these compounds and medicaments containing one of such compounds and, optionally, a second antiviral agent, especially a reverse transcriptase inhibitor, such as ddC, AZT or ddI, TIBO derivatives, tricyclic diazepinones, a HIV-protease inhibitor, α-, β- and/or γ-interferon, interleukin-2 and/or GM-CSF, and

the use of these compounds for the manufacture of medicaments especially for the treatment or prophylaxis of viral infections, particularly of retroviral infections, such as HIV 1 and/or HIV 2 infections, or for protecting cells against such infections.

All the tautomeric and stereoisomeric forms of the compounds of formula I are included in the scope of this invention.

Pharmaceutically acceptable salts may be those with organic acids, e.g. lactic, acetic, malic or p-toluenesulfonic acid; or salts with mineral acids, such as hydrochloric or sulfuric acid.

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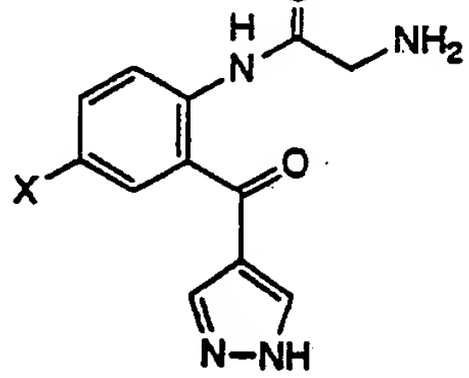
The compounds of the invention can be prepared in a manner known per se, e.g. as described in US 3405122, 3398159, 3407211 and 3400128; in J. Org. Chem. 41, 1976, 2720; 35, 1970, 2455 and 46, 1981, 839; in Acta Chem. Scan. B 31, 1977, 701; in J. Heterocyclic Chem. 12, 1975, 49 and 25, 1988, 1293; in Synthesis 1988, 767; in Syn. Commun. 15, 1985, 1271 and J.A.C.S. 100, 1978, 4842.

Thus the compounds of the invention can be prepared by cyclizing a compound of formula

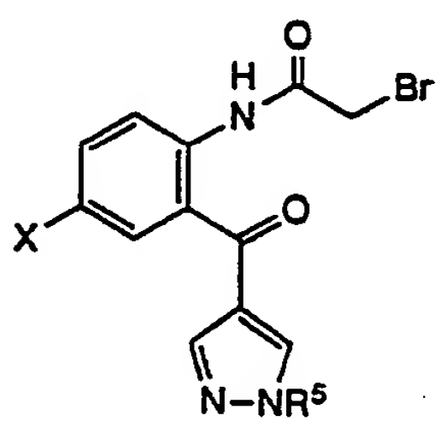


V

wherein X is as above,
by acid-catalysis.

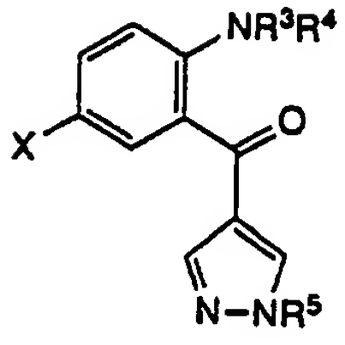
This cyclization can be performed by heating the compound V with an acid, such as pivalic acid, in a solvent, such as toluene and THF, or in n-butanol, at a temperature up to reflux temperature.

The amines V can be prepared via the corresponding bromides IV



IV

starting from ketones of formula III



III

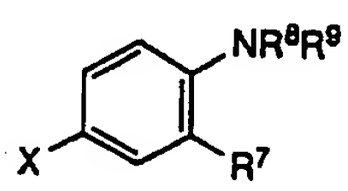
wherein X is as above and R^3, R^4 and R^5 are H or a N-protecting group.

Suitable N-protecting groups include triphenylmethyl, acyl, trialkylsilyl, alkyldiarylsilyl, ethoxymethyl, (dialkylamino)methyl, t-butoxycarbonyl and phenoxycarbonyl. A preferred method for performing the reaction III→IV→V involves bromoacetylation of a ketone III to the bromide IV, followed by ammonolysis to the amine V.

The ketones III can be prepared by reacting a metallo-heterocycle of formula VI

$$R^6\text{-}Z \qquad \text{VI}$$

where Z is the same R^5 substituted pyrazolyl group as in the compounds of formulae III and IV above, except that one or both hydrogens on the C-atoms in this pyrazolyl group may be replaced by an unreactive blocking group; and R^6 is a metal or a metallic halide group, such as MgBr, MgCl, Li, Na or Sn, with an aromatic compound of formula VII



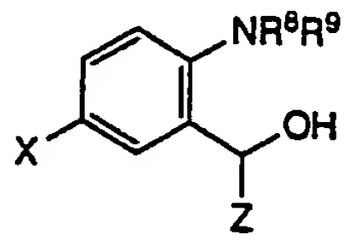
VII

where R^7 is formyl or a functional derivative of a carboxylic acid, such as cyano, ester, amide or acyl chloride, X is as above and R^8

and R^9 are H, O, acyl, trialkylsilyl, alkyldiarylsilyl or t-butoxy-carbonyl.

In formula VI above, preferable unreactive blocking groups include halogen, S-lower alkyl, S-aryl, trialkylsilyl and alkyldiarysilyl.

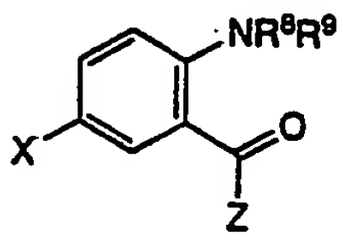
When R^7 is formyl, an alcohol of formula VIII is generated



VIII

where X, Z, R^8, and R^9 are as defined above.

When R^7 in formula VII is other than formyl, a ketone of formula IX is obtained



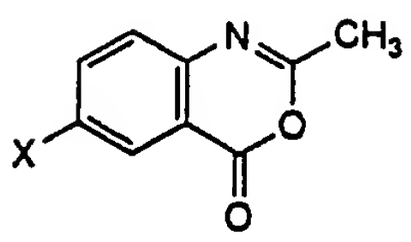
IX

where X, Z, R^8 and R^9 are as defined above.

The conversion of VIII to IX can be accomplished by oxidation, e.g. catalytic oxydation or reaction with active maganese dioxide.

Compound IX is then converted to the desired compound of formula III using conventional methods, e.g. as described in the Examples.

Similarly, a compound of formula VI is reacted with a compound of formula X



X

where X is as above, to generate the desired ketone IX wherein R^8 is H and R^9 is acetyl.

The compounds I and their salts have useful antiviral, especially anti-retroviral activity, particularly against HIV, the virus implicated in the development of AIDS and related diseases such as ARC (AIDS related complex). These compounds also inhibit HIV replication by inhibiting such important HIV viral functions as TAT (transactivating transcriptional) activity.

The compounds of formula I were tested for anti-HIV-TAT activity in an assay comprising the following steps:

(a) putting both the expression of the Secreted Alkaline Phosphatase (SeAP) gene and the viral transactivator TAT gene under the control of the HIV promoter LTR responsive to the action of the HIV transactivator TAT;

(b) transfecting cultured mammalian cells with plasmids which contain the gene constructs of (a) above and cause cellular production of the transactivating factor TAT and SeAP;

(c) adding the agent to be tested, here the compounds of formula I; and determining the amount of SeAP produced, by measuring SeAP enzymatic activity, whereby inhibition of SeAP production correlates with the anti-TAT inhibition activity.

In this assay, the inhibition of SeAP positively correlates with anti-TAT activity. The greater the ability of an agent to inhibit SeAP, the greater is its anti-TAT activity.

Specifically, with respect to the results reported below, the anti-HIV-TAT assay was run as follows:

At 24 hours post transfection 1, 10, 25 and 50 μM of a test compound of formula I was added to the culture media of COS cells transfected with two plasmids, one containing the reporter gene which codes for SeAP under control of HIV-LTR, and the other containing the HIV-TAT gene also under control of HIV-LTR. The alkaline phosphatase activity of the media was assayed 48 hours after addition of test compound with a colorimetric assay using p-nitrophenylphosphate as the substrate. The anti-TAT activity is measured by the percent inhibition of SeAP gene expression under the control of HIV-LTR versus the percent inhibition of SeAP gene under RSV-LTR, which does not respond to TAT.

The results in the Table below show that the compounds of formula I are specific inhibitors of HIV-TAT-regulated gene expression without non-specific cytotoxic effects.

The specificity of the compounds of formula I as TAT inhibitors was demonstrated with a parallel assay in which the SeAP gene expression is put under control of the Rous sarcoma virus (RSV)-LTR which does not respond to TAT. This assay thus eliminates the possibility that the compounds of formula I are either general cytotoxic agents or inhibit the activity of SeAP.

The anti-HIV-TAT activities of the test compounds were determined by measuring the amount of alkaline phosphatase in the supernatant media of cultures of cells in which SeAP gene expression was under the control of the HIV LTR promoter. The specific inhibitory activities of the test compounds were calculated according to the formula:

$$100\ [(1-A/B) - (1-C/D)]$$

where A and B are the alkaline phosphatase activites produced by HIV-LTR/SeAP in the presence and absence, respectively, of test compound, and C and D are the alkaline phosphatase activities produced by RSV-LTR/SeAP in the presence and absence, respectively, of test compound. The concentrations tested ranged from

1-50 µM. The results provided are the average of at least three tests. The test compound was added 24 hours after cells were transfected with the plasmids when SeAP specific mRNA and protein were already present and the protein was very stable. Therefore, 100% inhibition would not be observed with this assay procedure.

Table

Product of Example No.	Anti-HIV-TAT activity
1	High
3	High

With respect to human patients infected with HIV, and patients with symptomatic or asymptomatic HIV infections, an antivirally-effective amount of a compound of formula I or a salt thereof is in the range of from about 0.5 to 40 mg/kg, preferably from about 1 to 15 mg/kg, more preferably from about 4 to 10 mg/kg body weight per day. In unit dosage form, for a 70 kg patient, this would be an amount of from about 35 to 2800, preferably from about 210 to 350 mg per day. This dosage may be administered parenterally or orally in one or more doses at various intervals daily, preferably orally once daily.

The compounds may also be administered with other antiviral and/or biological response modifiers. For example, the compounds of formula I may be administered with known HIV-RT inhibitors such as ddC, AZT, ddI or non-nucleoside RT inhibitors such as TIBO derivatives or tricyclic diazepinones, or other inhibitors which act against other HIV proteins such as protease, integrase and RNAaseH, as well as with biological modifiers such as α-, β- or γ-interferon or a combination thereof, interleukin-2 and GM-CSF. The dosages of ddC and AZT used in AIDS or ARC human patients have been published. When given in combined therapy, the other anti-HIV compounds may be given at the same time as a compound of formula I or the dosing may be staggered as desired. The two (or more) drugs may also be

combined in a composition. Doses of each drug may be less when used in combination than when they are used as a single agent.

It is possible for the compounds of the invention to be administered alone in solution. However, it is preferred that the active ingredients be administered in a pharmaceutical formulation or composition. These formulations comprise at least one active ingredient together with one or more pharmaceutically acceptable carrier and excipient and may optionally include other therapeutic agents, for example a protease inhibitor. These carriers include those suitable for oral, rectal, nasal, topical, buccal, sublingual, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

Examples of compositions of the invention are solutions of the active ingredient(s), e.g. in water or saline; capsules, e.g. soft gelatine capsules; sachets or tablets, each containing a pre-determined amount of the active ingredient, e.g. as granules; solutions or suspensions in an aqueous liquid or in an oil-in-water emulsion or a water-in-oil liquid emulsion. Tablets may include one or more of lactose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, stearic acid and other excipients, colorants and pharmacologically compatible carriers. Formulations suitable for topical administration include lozenges comprising the active ingredient in a flavor, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising cocoa butter or a salicylate. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gells, pastes, foams or spray formulas. Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended

recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example ampules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules and tablets of the kind previously described.

Example 1

a) A mixture of 4-bromo(1H)-pyrazole (50.8 g) (described in U.S. Patent No. 2,992,163), 1300 ml of CH_2Cl_2, triphenylmethyl chloride (99,5 g) and Et_3N (35.3 g) was stirred at room temperature for 24 hours. The solution was then extracted with H_2O, dried over $MgSO_4$, filtered and evaporated to give a solid residue. Crystallization with CH_2Cl_2/Hexane provided white crystals: mp. 190-192°C. A second crop was taken to provide a total of 117.3 g (84%) of 4-bromo-1-(triphenylmethyl)-1H-pyrazole.

b) A mixture of 4-bromo-1-(triphenylmethyl)-1H-pyrazole (48 g), Et_2O (100 ml) and THF (500 ml) were stirred at -78°C under a stream of argon. tBuLi (160 ml, 1.7M) was added to the mixture, and the resultant solution was stirred for 2.5 hours at -78°C. At that time, the solution was added to a solution of 2-methyl-6-chloro-4H-3,1-benzoxazin-4-one (21 g) in THF (500 ml) which had been cooled to -78°C. The mixture was allowed to warm to room temperature overnight, and then quenched with saturated NH_4Cl solution (350 ml). After dilution with EtOAc (500 ml), the layers were separated, and the organic layer washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated. The solid residue was combined with THF (400 ml), MeOH (350 ml), H_2O (250 ml) and 10N NaOH (300 ml), and stirred at reflux temperature for 3 hours. After cooling to room temperature, the organic and aqueous phases were separated. The aqueous phase was extracted with Et_2O and the combined organic

fractions dried over $MgSO_4$, filtered and evaporated to give a foam. This material was combined with CH_2Cl_2 (1 liter) and stirred overnight. After filtration, the filtrate was evaporated to afford 49 g of a viscous yellow oil.

c) To a stirred mixture of the product of b) above, THF (450 ml), CH_2Cl_2 (450 ml), and 1N NaOH (1400 ml) were added dropwise at room temperature. The two-phase mixture was stirred at room temperature for 20 minutes. After separation of the layers, the aqueous layer was further extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from THF (100 ml), and hexane (300 ml) to afford 23.5 g of 2-bromo-4'-chloro-2'-[(1-triphenylmethyl)-1H-pyrazol-4-yl]-carbonyl]acetanilide, mp. 197-200°C.

d) To 1 liter of condensed liquid ammonia in a dry-ice bath was added a solution of the product of c), in THF (200 ml). The mixture was stirred overnight and the ammonia allowed to evaporate. Residual solvent was distilled off. The dried residue was stirred with EtOAc (450 ml) and H_2O (600 ml). The product was collected, washed with water and dried to give 18.3 g of a solid.

e) A suspension of this material in 1-butanol (600 ml) containing 300 mg of pivalic acid was heated to reflux temperature for 8 hours. Additional portions of 300 mg each of pivalic acid were added after 3 hours and 5 hours. Volatiles were evaporated, and trituration of the dry residue yielded 6.5 g of product. This was dissolved in MeOH (600 ml), treated with charcoal, filtered and concentrated. The precipitated product was collected to give 5.25 g of 7-chloro-1,3-dihydro-5-(1H-pyrazol-4-yl)-2H-1,4-benzodiazepin-2-one, mp. 289-291°C.

Example 2

The product of Example 1e) can also be prepared as follows:

a) The product of Example 1a) (24 g) was combined with THF (400 ml) and Et_2O (100 ml) and cooled to -78°C under argon. tBuLi (80 ml, 1.7M) was added dropwise to the mixture, and the resultant solution stirred at -78°C. A solution of 5-chloro-2-nitrobenzaldehyde (11.2 g) in THF (150 ml) was added dropwise to the stirred solution, and the resultant mixture allowed to warm to room temperature overnight. After quenching with saturated NH_4Cl solution, the mixture was diluted with EtOAc, and the layers separated. The organic fraction was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated. Flash column chromatography using a gradient elution system from 10% EtOAc/hexane to 75% EtOAc/hexane provided 20.6 g of α-(5-chloro-2-nitrophenyl)-1-(triphenylmethyl)-1H-pyrazole-4-methanol, MS 495 (M^+).

b) A mixture of the product of a) above (27.1 g), $CHCl_3$ (250 ml) and MnO_2 (20 g) was stirred at reflux temperature for three hours. An additional aliquot of MnO_2 (5 g) was added, and the mixture stirred five hours. After cooling, the mixture was filtered and evaporated to provide 26.9 g (5-chloro-2-nitrophenyl) [1-(triphenylmethyl)-1H-pyrazole-4-yl]methanone, MS 493 (M^+).

c) A mixture of the product of b) (26.9 g), EtOH (400 ml) and 4N HCl (100 ml) was combined and stirred at reflux temperature. After neutralization with 30% NaOH at 0°C, the EtOH was evaporated and the resultant aqueous phase extracted with EtOAc. The organic fractions were dried over $MgSO_4$, filtered and evaporated. The residue was purified by filtration through silica gel using a gradient elution system from 30% EtOAc/hexane to 100% EtOAc to yield (5-chloro-2-nitrophenyl)(1H-pyrazol-4-yl)methanone. This was combined with EtOH and 10% Pd/C and hydrogenated. Flash column chromatography afforded 10 g of (2-amino-5-chlorophenyl)-1H-pyrazol-4-ylmethanone, MS 221 (M^+).

d) To a solution of the product of c) (10.5 g) in THF (300 ml) and CH_2Cl_2 (300 ml) was added $NaHCO_3$ (25 g) and an ice-water mixture (300 ml). The stirred mixture was treated with 37.2 ml $BrCOCH_2Br$. The two phases were separated, and the aqueous phase extracted with CH_2Cl_2. The organic fractions were dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in THF (100 ml) and added to liquid NH_3 (200 ml), which has been cooled to -78°C, and allowed to stir overnight while warming to room temperature. The volatiles were evaporated and the residue partitioned between EtOAc and H_2O. After separation of the layers, the aqueous fraction was extracted with EtOAc. The organic fractions were dried over $MgSO_4$, filtered and evaporated. The residue was combined with 1-BuOH (100 ml) and pivalic acid (75 mg) and the mixture heated to reflux temperature. The solvent was removed by evaporation, and the product purified by flash column chromatography (6.5% MeOH/CH_2Cl_2) to provide 5.5 g of 7-chloro-5-(1H-pyrazol-4-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

Example 3

a) Bromopyrazole (24.0 g) was suspended in dry THF (600 ml) and cooled in dry ice-acetone bath with stirring under an argon atmosphere. n-Butyllithium (2.5M in hexane, 24 ml) was added drop-wise. After 2 hours, the solution was added to 2-methyl-6-methyl-4H-3,1-benzoxazin-4-one (8.76 g) (prepared according to J. Chem. Soc.,. 1954, 4676) in THF (500 ml), pre-cooled to -50°C. The reaction was quenched after stirring for 20 minutes by addition of 15% NH_4Cl in water (w/v, 300 ml) and allowed to warm to room temperature. The mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride. The aqueous layers were washed with EtOAc. The organic layers were combined, dried, filtered, and concentrated. The resulting solid was suspended in a mixture of THF (300 ml), methanol (350 ml), water (250 ml) and 10N sodium hydroxide (270 ml), and heated at reflux temperature with stirring. The mixture was allowed to cool to

room temperature, and partitioned between ether and water. The organic layers were washed with saturated aqueous sodium chloride, then combined, dried, filtered, and concentrated. The residue was suspended in CH_2Cl_2 and filtered. The filtercake was washed with CH_2Cl_2. The filtrate was concentrated and passed through silica gel using EtOAc-CH_2Cl_2 mixture (1:9 v/v) as eluant. The eluant was concentrated and the residue crystallized from CH_2Cl_2-hexane to give 15.18 g of (2-amino-5-methylphenyl)[1-(triphenylmethyl)-1H-pyrazol-4-yl]methanone. MS Calcd: 443, 1997; Found: 443, 1990.

b) The product of a) (2.85 g) was dissolved in a mixture of THF (150 ml) and ether (150 ml) and cooled in an ice-water bath. Saturated aqueous sodium carbonate (100 ml) was then added. Bromoacetyl bromide (4 x 0.67 ml, 30.9 mmol) was added with stirring. After 4 hours, the reaction mixture was diluted with water and extracted with EtOAc. The precipitate formed was collected by filtration and dissolved in CH_2Cl_2. The EtOAc fraction was combined with the CH_2Cl_2 solution and dried, filtered, evaporated, and concentrated, and the residue crystallized from CH_2Cl_2-hexane to yield 3.33 g of 2-bromo-N-[4-methyl-2-[[1-(triphenylmethyl)-1H-pyrazol-4-yl]carbonyl]phenyl]acetamide, MS Calcd: 563.1208; Found: 563.1188.

c) The product of b) (2.26 g) was dissolved in CH_2Cl_2 (100 ml) and cooled in a dry ice-acetone bath. Liquid ammonia (50 ml) was then condensed into the reaction mixture. The resulting solution was stirred and allowed to warm to room temperature. After addition of water and mixing, the layers were separated. The organic layer was extracted with saturated aqueous sodium bicarbonate. The aqueous layers were washed with CH_2Cl_2. The CH_2Cl_2 layers were dried, filtered and concentrated. The residue was recrystallized from CH_2Cl_2-hexane to give 1.68 g of 2-amino-N-[4-methyl-2-[[1-(triphenylmethyl)-1H-pyrazol-4-yl]carbonyl]phenyl]acetamide. MS Calcd: 501.2291; Found: 501.2272.

d) A suspension of the product of c) (15.02 g) in nBuOH (300 ml) was heated at reflux with stirring. After cooling to room temperature, the reaction was concentrated to dryness. The residue was suspended in THF and heated to reflux. The resulting suspension was filtered, the filtercake was washed with THF. The filtrate was combined, washed and heated at boiling temperature and concentrated. The resulting mixture was allowed to cool to room temperature and allowed to stand for 3 hours. The product was washed with THF and dried yielding 5.50 g of 1,3-dihydro-7-methyl-5-(1H-pyrazol-4-yl)-2H-1,4-benzodiazepin-2-one, mp. 282-289°C.

The following galenical compositions containing a compound I or a salt thereof as active ingredients as defined above, can be prepared in a manner known per se:

a) Oral liquid formulation:

Ingredients	mg/formulation
Active ingredient	20.0 mg
Methylparaben	20.0 mg
Sucrose	q.s.
Flavoring agent	q.s.
Citrate buffer	q.s.
Purified water q.s.	5.0 ml

b) Tablet formulation:

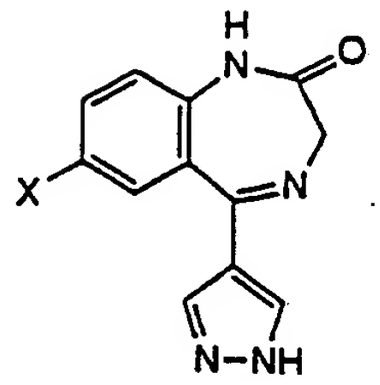
Ingredients	mg/tablet
Active ingredient	20 mg
Starch	40 mg
Avicel	80 mg
Lactose	274 mg
Magnesium stearate	2 mg
	416 mg

c) Soft gelatine capsule formulation:

Ingredients	mg/capsule
Active ingredient	20 mg
Ethoxylated Fatty acids	500 mg
PEG 4000	100 mg
Vegetable oils q.s. to	1.0 ml

CLAIMS:

1. Benzodiazepinones of formula



I

wherein X is Cl or CH_3,

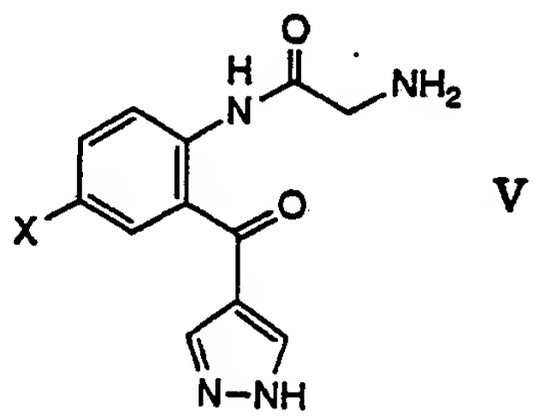
and pharmaceutically acceptable salts.

2. 7-Chloro-5-(1H-pyrazol-4-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

3. 7-Methyl-5-(1H-pyrazol-4-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

4. A compound according to claim 1, 2 or 3 for use as a therapeutically active agent, especially for the treatment or prophylaxis of viral infections, particularly of retroviral infections, such as HIV 1 and/or HIV 2 infections, or for protecting cells against such infections.

5. A process for preparing a compound as in claim 1, which comprises cyclizing a compound of formula



V

wherein X is as in claim 1,

by acid-catalysis.

6. A medicament, especially for the treatment or prophylaxis of viral infections, particularly of retroviral infections, such as HIV 1 and/or HIV 2 infections, or for protecting cells against such infections, containing as active pharmaceutical ingredient a compound as in claim 1, 2 or 3, and, optionally, a second antiviral agent, especially a reverse transcriptase inhibitor, such as ddC, AZT, a HIV-protease inhibitor, α-, β- and/or γ-interferon, interleukin-2 and/or GM-CSF.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00352

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/04; A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,3 400 128 (L. BERGER ET AL.) 3 September 1968 see column 1 - column 5; example 7 ---	1,4,5
P,X	EP,A,0 491 218 (F. HOFFMAN-LA ROCHE) 24 June 1992 see page 7 - page 8; claims -----	1,4-6

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26 APRIL 1993	11. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	FRANCOIS J.C.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300352
SA 70328

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 26/04/93

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